Protein folding: from simplified models to the design of folding inhibitors.

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• protein folding
• results from simplified models
• one slide on the computational algorithm
questions:  
• how can such a complicated system display a unique (S=0) equilibrium state?  
• how can folding be so fast?  
• what is the native state of a given sequence?  
• what is the effect of mutation? are there other stable conformations? etc…
The source of all problems: the interactions within proteins are frustrated

random sequence

sequence selected by evolution (Δ >> δ)

Residual frustration:
- still complicated to predict the N state
- protein marginally stable (ΔF ≈ 10 kT_{room})
- kinetics easily trapped
Folding simulations

- bond & angle vibrations
- motion of the sidechain
- formation of $\alpha$-helices
- formation of $\beta$-hairpins
- hydrophobic collapse
- diffusion of protein segments
- folding

- quantum description
- classical, all-atom, explicit solvent
- simplified
Simplified models

• simplified degrees of freedom
• potential tuned to reproduce some experimental data

\[ U = \sum_{i<j} B_{ij} \left[ \left( \frac{r_0}{r_{ij}} \right)^{12} - 2 \left( \frac{r_0}{r_{ij}} \right)^{6} \right] \]

• native state as ground state

\[ B_{ij} > 0 \text{ only if } i \text{ and } j \text{ are close in the native conformation.} \]

(automatically cooperative transition)

• reproduce effects of mutations on the stability of the native state \( \Delta \Delta F_{UN} \)

\[ \rightarrow \text{ obtain a set of } B_{ij} \text{ from the } \Delta \Delta F_{UN} \text{ tabulated for each site.} \]

simulation algorithm: metadynamics (at the end...)
Limelight on the denatured state

Is the denatured state a random coil?
calculate the “nativeness” $q_i$ of the sites in the denatured state

- there is a lot of native structures in the denatured state.
- this agree with recent NMR data (e.g. Klein-Seetharaman et al. Science 2002).
- this stable structures form a nucleus and are related to the transition state.
Idea from simple models!

 coil

 Folding nucleus

Free energy

D

N
Idea from simple models! …to inhibit a protein by destabilizing its native state

use a peptide with the same sequence as such critical segments to block the formation of the folding nucleus.

\[ \Delta F_{N-D'} = \Delta F_{\text{folding}} - E_{\text{dock}} - TS_{\text{dock}} \]

Advantages:
- the protein itself suggests its inhibitor
- unlikely to induce resistance
Testing the idea: lysozyme

Protein sequence: KVFGRCelAAAMKRHGLDNYRGYSLG... ...MKRHGLD

- Pep 1 (1-10)
- Pep 2 (6-15)
- Pep 25 (121-129)

Surely unfolded by NMR

Surely folded

Helix 91-100
A more interesting case: HIV-1 protease

peptide 83-93

$k_i = 2.58 \pm 0.7 \mu M$
Metadynamics

• select few slow-varying “collective variables” of the system.
• add a non-Markovian term to the Hamiltonian which disfavours the sampling of regions already visited.

Thanks....

Who did the job...

**experiment**
- Martina Caldarini
- Francesca Vasile

**theory**
- Ludovico Sutto
- Carlo Camilloni
- Davide Provasi (now at Mount Sinai University, NYC)
- Franz Marini
- Ricardo A. Broglia
- GT